REMARKS

Claims 1-10 have been canceled.

Claims 12-15 have been withdrawn.

New claim 25 finds its support in the specification on Page 19, lines 18-20.

No new matter has been added.

Rejections Under 35 USC § 112, Second Paragraph

The Examiner contends that the units of viscosity used in the application, i.e. "Pa*sec^{-1}" are not standard and that one of ordinary skill would not understand what the claims define. She requires documentation as to how this unit of measure converts to more standard measures used in the art.

Applicants first point out that this unit of measure, Pascal-second, is indeed standard, although the unit "poise" (abbreviated as "p") is also a standard measure that is used. In the U.S., Pascal-second is currently written as Pa·s; Applicants wonder whether the Examiner is confused because Applicants have used an asterisk "*" instead of a dot "·" to show the relationship. Regardless, Applicants have submitted the following references that define this term: Reference 1 = Spe antec 1998 Proceedings page 936 (1998: Spe, Carlstedt and Stanaszek, CRC Press; note that this reference also uses an asterisk "*" to denote the relationship); Reference 2 = Viscosity-Wikipedia; Reference 3 = Fluid Dynamics Lab Transport Phenomena, Fluid Flow, Rheology; Reference 4 = Brookfield Viscosity Glossary and Reference 5 = Google Calculator.

The physical unit of dynamic viscosity, which is often referred to as simply "viscosity," is the Pascal-second (i.e. Pa*s or Pa·s; see page 2 of Reference 2). The relationship between Poise and Pascal-second is 1cP=1m Pa*s (see Reference 2, page 3, lines 13-15). Reference 2 teaches that some fluids viscosity is a constant over a wide range of shear rates while for other fluids the viscosity changes with the shear rate. These inconstant-viscosity fluids are called Non-Newtonian fluids. Reference 3 also refers to Non-Newtonian fluids on page 3 and confirms that the viscosity of these fluids is dependent on both temperature **and on shear rate**. Hyaluronic acid is a Non-Newtonian fluid. Therefore, since hyaluronic acid is a Non-Newtonian fluid, the instant application must measure viscosity taking into consideration the shear rate. This results in the Non-Newtonian viscosity unit of Pa*s at a shear rate of 1 per second (1 s^{-1}) or Pa*sec^{-1}.

Applicants point out that the Huang prior art reference cited by the Examiner refers to this at column 3, line 67 where he shows that the viscosities of the crosslinked gels are determined in cps (i.e. centipoises) at room temperature and at a shear rate of 1 sec^{-1} for viscosities greater than 6000 cps. Consequently, the Huang crosslinked gels can be "translated" into Pa*s units simply by using the conversion factor of 1cp = 1mPa*s or stated differently, 6000 cps = 6 Pa*s. This allows easy comparison between the viscosity of the Huang reference and the viscosities of the instant invention.

Applicants respectfully submit that they have provided the Examiner with the required documentation as to how the Pa*sec^{-1} unit used in the instant application converts to "more standard measures" used in the art, thereby overcoming the rejection. Thus, Applicants request removal of the rejection.

Rejections Under 35 USC § 103

Della Valle in view of Malson and Huang

The Examiner has rejected claims 11, 16, 19 and 24 as obvious over Della Valle et al (EP 341745) in view of Malson et al (US 5,783,691) and Huang et al. (US 5,532,221). The Examiner contends that Della Valle teaches a 5% autocrosslinked derivative of hyaluronic acid (HA) and the use of the product in a variety of forms and teaches that the products are "similar to those already known and commercially available or described in the literature" suggesting their use as replacements for similar products known in the art. The Examiner acknowledges that the reference is silent regarding the prevention of surgical adhesions. The Examiner concludes that "the use of crosslinked HA for this purpose is known generally in the art."

The Examiner contends that Malson teaches that covalently crosslinked HA derivatives are known generally to be useful in medical applications, such as prevention of surgical adhesions. The Examiner acknowledges that the reference is specifically drawn to HA that is crosslinked through phosphate ester linkages. She further contends that the reference teaches the use of this product as a slow-release form of HA useful for the applications known for HA and other crosslinked HA derivatives. Lastly, The Examiner contends that the reference teaches that its product is superior to other known crosslinked Has because it introduces fewer "alien" products that may result in immunological or inflammatory reactions.

The Examiner contends that Huang teaches the use of ionically crosslinked HA for the prevention of surgical adhesions, administration of the product in a variety of surgical procedures and in combination with a number of anti-adhesion therapeutic agents. She further contends that

this reference teaches that the efficacy of the product in preventing adhesions is a function of the viscosity and degree of crosslinking.

The Examiner concludes that it would have been obvious for the skilled artisan to use the Della Valle products for the prevention of post-surgical adhesions and that one would have a reasonable expectation of success in so doing because Malson and Huang teach that HA and crosslinked HA derivatives are known to have this utility. In addition, the Examiner states that the skilled artisan would be further motivated to use this product because it is crosslinked without incorporating into the covalent structure chemicals that could produce undesirable immunological/inflammatory reactions.

As to the surgery, the Examiner concludes that the references teach the problem of adhesion formation in general during surgery and that Huang teaches a few species. Here she concludes that the skilled artisan would administer this product in any type of surgery with a reasonable expectation of success.

With regards viscosity, degree of crosslinking and molecular weight, the Examiner reasons that Huang teaches that the efficacy of the product is a function of viscosity and degree of crosslinking, and that Della Valle teaches the preparation of 5% crosslinked products and that viscosity is a function of molecular weight and concentration. From this the Examiner concludes that the prior art teaches how to prepare a product for optimal anti-adhesion properties and that optimizing this through routine experimentation would be done with a reasonable expectation of success. Her final conclusion here is "this is exactly consistent with what is known in the art and does not appear to be unexpected."

Applicants respectfully traverse.

Applicants have previously stated that the Della Valle reference, while disclosing autocrosslinked hyaluronic acid derivatives, provides no guidance as to the degree of viscosity that is necessary to achieve fewer adhesions than the untreated controls. In fact, the Della Valle patent does not even contain the term "viscosity." The Malson reference does not fill this void in discussing viscosity, and likewise does not address the need for highly viscous derivatives.

As stated in the past, the Examiner states that Malson teaches that HA and crosslinked HA derivatives are known **generally** to be useful in medical applications. But this does not mean that all HA derivatives and crosslinked derivatives are useful for each and every purpose; this concept is exemplified in Study 8 beginning on page 52 of the Specification.

The Examiner now adds the Huang reference to try to fill the gaps that remain after combining the Della Valle and Malson references – i.e. the importance of viscosity. To do this she points to the Huang reference concluding that it teaches that efficacy of the product in preventing adhesions is a function of the viscosity and degree of crosslinking. But adding Huang still does not provide the expectation of success that the Examiner needs in order to make a prima facie case of obviousness.

First, the Examiner's statement that the Huang reference teaches that the efficacy of the product in preventing adhesions is a function of the viscosity and degree of crosslinking is not correct. The Declaration by Dr. Anna Maria Zanellato (attached) explains why and is summarized below.

Dr. Zanellato points out that at column 4, lines 3-5 Huang teaches that the most preferred crosslinked gel to prevent adhesions is in the viscosity range of 2,500 cps (i.e. 2.5 Pa*s; see above) to 100,000 cps (i.e. 100 Pa*s). The instant application claims a gel with at least 200 Pa*s

or, using Huang's units, 200,000 cps. On page 5, Example 1-b uses HA crosslinked gel with 88,600 cps of viscosity (i.e. 88.6 Pa*s) in the testing protocol. Examples 2 and 4 use gels with 60,200 cps (60.2 Pa*s). Example 5 teaches that "*a clear trend towards improved efficacy with increasing crosslinking density* [i.e. degree of crosslinking] *was observed in ... Table 4*" (column 11, lines 32-34). In fact, Table 4 shows that 20% adhesions are produced from a gel with 1% degree of crosslinking and 1570 cps (i.e. 1.57 Pa*s) of viscosity while a gel having a 5% degree of crosslinking and 2560 cps (2.56 Pa*s) viscosity gives 62% adhesions. Therefore, as stated by Dr. Zanellato, these data teach that the % of adhesions is ***independent*** of a gel's viscosity.

Dr. Zanellato states that this aspect is clarified in Table 6 where it is evident how a gel with a 25% degree of crosslinking with a viscosity of 7660 cps (7.66 Pa*s) gives 49% adhesions while the gel with the same % of crosslinking but greater viscosity generates 91% adhesions. She also notes that, in addition, Table 6 shows that fewer adhesions (27%) are produced by a gel with 50% crosslinking and 8840 cps (8.84 Pa*s) whereas the gel with the higher viscosity (146,000 cps or 146 Pa*s) gives only 49% adhesions.

Dr. Zanellato states that this evidence is supported by Huang's conclusions where he affirms in column 11, lines 41+ that the efficacy of HA increases with the crosslinking density, i.e. the degree of crosslinking. Therefore, Dr. Zanellato concludes that this **reference teaches away** from a product's efficacy of adhesion prevention being determined by viscosity. She states that Huang actually teaches the contrary – that viscosity data are irrelevant in preventing tissue adhesions. Based on the evidence, Dr. Zanellato states that the Examiner's contention that the data disclosed in the Specification which shows that the ability of the instant product to prevent

adhesions with increases with viscosity is not unexpected results, but is "exactly consistent with what is known in the art and does not appear to be unexpected" is a wrong conclusion.

Similarly, Dr. Zanellato states that the Examiner's contention that the art teaches how to prepare a product for optimal anti-adhesion properties (page 5 of the current Office Action, lines 6-7) is incorrect. As just discussed, Huang teaches that only the degree of crosslinking matters and Della Valle teaches only the preparation of a 5% HA crosslinked gel, i.e. there is no discussion of viscosity. Dr. Zanellato points out that it is only in Study 8, which is presented in the instant application, that the role of viscosity in adhesion prevention is determined.

Thus, the combination of the Della Valle reference, the Malson reference and the Huang reference do not teach the instant invention or even suggest that viscosity is a critical feature. Instead, the references teach away from the instant invention. Consequently, Applicants respectfully request reconsideration and removal of the rejection.

Della Valle in view of Malson, Huang and Matsuda

The Examiner has rejected claims 11, 16, and 19-25 as obvious over Della Valle in combination with Malson, Huang and Matsuda (US 5,462,976). The Della Valle, Malson and Huang references are discussed above. The Examiner acknowledges that these references do not teach the range of forms listed in claim 19.

With respect to Matsuda, the Examiner contends that this reference also teaches that glycosaminoglycans, such as HA, are useful for the prevention of surgical adhesions as well as teaching that these crosslinked biopolymers may be prepared in a variety of forms.

The Examiner contends that it would have been obvious to the skilled artisan to prepare the Della Valle crosslinked HA material in any form known to be used for surgical applications with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, the Examiner has not made a prima facie case of obviousness because the prior art does not teach that the viscosity of the crosslinked HA is critical in its ability to prevent adhesions. Consequently, even considering the combined teachings with the Matsuda reference, which does not mention viscosity at all, use of the instant invention for prevention of post-surgical adhesions is not obvious as none of the references teach the importance of a viscosity of at least 200 $Pa*sec^{-1}$.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Della Valle in view of Malson, Huang and Dorigatti

The Examiner has rejected claims 11 and 15-25 as obvious over Della Valle in combination with Malson, Huang and Dorigatti (WO 94/17837). The Della Valle, Malson and Huang references are discussed above. The Examiner acknowledges that these references do not teach the use of a biomaterial comprising a non-biodegradable synthetic polymer.

The Examiner contends that Dorigatti teaches the use of a HA derivative in combination with various synthetic polymers and that this material has utility as an anti-adhesive product fur use in surgery.

The Examiner contends that it would have been obvious to the skilled artisan to modify the Dorigatti product by use of the Della Valle crosslinked HA material and to use it for

prevention of surgical adhesions with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, the Examiner has not made a prima facie case of obviousness because the prior art does not teach that the viscosity of the crosslinked HA is critical in its ability to prevent adhesions. Consequently, even considering the combined teachings with Dorigatti, which similarly does not discuss viscosity, the use of the instant invention for prevention of post-surgical adhesions is not obvious as none of the references teach the importance of a viscosity of at least 200 $Pa*sec^{-1}$.

Thus, Applicants respectfully request reconsideration and removal of the rejection.

Accordingly, in view of the above amendments and remarks, reconsideration of the rejections and allowance of the claims of the present application are respectfully requested. In the event that the Amendment does not place the present application into condition for allowance, entry thereof is respectfully requested as placing the present application into better condition for appeal.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman (Reg. No. 47,604) in San Diego, CA at telephone number 858-792-8855 to conduct an Interview in an effort to expedite prosecution in connection with the present application.

The Commissioner is hereby authorized to charge Deposit Account No. 02-2448 in the amount of $120 for the one month extension of time fee according to 37 CFR § 1.17(a)(1).

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Dated October 18, 2007

Respectfully submitted,

#47,604

By _____
Leonard R. Svensson
Registration No.: 30,330
BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747
Falls Church, VA 22040-0747
(858) 792-8855
Attorney for Applicant

Enclosures: Carlstedt and Stanaszek reference (Reference 1)
Viscosity-Wikipedia reference (Reference 2)
Fluid Dynamics Lab Transport Phenomena, Fluid Flow, Rheology reference (Reference 3)
Brookfield Viscosity Glossary reference (Reference 4)
Google Calculator reference (Reference 5)

Declaration of Dr. Anna Maria Zanellato